TIME—A FOURTH DIMENSION OF PATIENTS*

The Anniversary Discourse

C. SIDNEY BURWELL

Samuel A. Levine Professor of Medicine, Harvard University Medical School; Physician to the Peter Bent Brigham Hospital and Visiting Physician to the Boston Lying-in Hospital

IT IS a great honor and pleasure to be asked to give the Anniversary Discourse to The New York Academy of Medicine. I am grateful for the opportunity.

Your distinguished President, when he first spoke about this, imposed certain restrictions on the speaker. The most definite of these clearly had to do with the length of the discourse, but he also suggested that this was not an occasion for the presentation of technicalities of research, but rather for a discussion of some broad principle, applicable to medicine but dealing with its philosophy rather than with its details. It has occurred to me, therefore, to present for your brief consideration an aspect of patients which is obvious enough but seldom discussed—namely, the factor of time or, more specifically, *the time in his own life when the patient is seen* as part of his description.

There is wide acceptance of the fact that physiological differences exist between different people. The Declaration of Independence says clearly "All men are created equal" but this need not, and should not, be taken to indicate that these equals are identical. Human beings, equal in fundamental importance as individuals, are indeed diverse in their characteristics, and those diversities have important significance for the occurrence, the progression, and the management of disease and disability.

This is all obvious, but it is not always as clearly understood that a given individual observed at one time may exhibit sharp differences as compared with himself at another time. Perhaps I can illustrate this concept by reminding you of a musical comedy hero who played his

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role so long ago that I am afraid few of you here had the pleasure of seeing him. I recall that he came on the stage to find a sideboard laden with drink, poured himself a libation, consumed it, and then said, "This makes a new man of me." Following this his face became thoughtful and then brightened as he said, "Give the *new man* a drink." These observations showed clearly that he understood that an organism could change with the passage of time and with the alteration of circumstances.

Following the classical work of Claude Bernard in the middle nineteenth century and of L. J. Henderson, Walter Cannon, and others in recent years, we are all strongly and properly impressed with the beautiful and generally effective mechanisms of homeostasis. These mechanisms have an extraordinary capacity to maintain the internal environment as a relatively stable one. It should be remembered, however, that in certain situations the levels of various bodily functions are reset at new points much as we set the thermostats in our houses at different levels to meet new conditions. Under these circumstances, homeostatic mechanisms continue to operate, but the definition of the internal environment has been altered.

Some of the conditions which lead to a change in the internal environment are imposed from without, and one can think of many instances in which disease establishes a new level about which a given function may fluctuate. Often, however, such changes occur as parts of normal healthy life, and it is with these that we are to be concerned tonight. I will ask you to consider in a somewhat superficial and postprandial manner some of the changes in the physiology of the human organism associated, first, with the aging process, second, with the state of pregnancy, and, third, with that beneficial and recurrent phenomenon called sleep.

The changes that occur with these natural events are extensive enough and impressive enough to make it fair to say that during these states we are actually dealing with a different kind of organism. These changes are often sufficient to alter the reactions of the body to such a degree that they influence for worse or for better the incidence and course of disease.

There is certainly nothing new about the point of view that *external* events can alter the responses of the human organism at different times. This belief is clearly embedded in folklore as well as in medical litera-

ture. In the "Golden Bough" Frazer refers to the deep impression made on dwellers near the sea by the ceaseless ebb and flow of the tides. He says, "The belief that most deaths happen at ebb tide is said to be held along the East coast of England from Northumberland to Kent."

Tonight, however, we are concerned not with influences, whether chemical, bacteriological, or sidereal, which are imposed from without, but with those imposed by fundamental, and to some degree, built-in rhythms which are part of the organism's original equipment. We have chosen as our examples aging, pregnancy, and sleep. In discussing these we shall be concerned primarily with physiology, although as in most conversations among doctors, medicine will keep breaking in.

The fact is familiar to all that growth, development, and aging do, over the years, profoundly alter organisms. Dr. John Lovett Morse used to say to his students when he taught pediatrics in the Harvard Medical School, "A baby is not a little man." He wanted us to learn, I think, that infants and children are qualitatively and quantitatively different from young adults and from the aged. We know that growth, development, and involution produce changes in the physiology of the human organism, quite aside from wear and tear. We can all think of examples of the differences that exist in these groups. In youth the oxygen consumption per square meter is higher and it tends to fall progressively with advancing age. The processes of growth and development and the youthful expenditures of energy call for more food than in later years. One definition of youth—I think from "Three Men in a Boat"—is based on the experiment of offering a large soggy bun to the subject fifteen minutes before dinner. If it is accepted the diagnosis of youthfulness may be made.

Obviously the amounts and relationships of hormones are different in youth and age and it is not surprising that the same person at different ages is a different organism in his response to disease. Think, for example, of the variations in the course of acute rheumatic fever, or acute nephritis, or measles when these disorders occur in different age groups. When pernicious anemia or gout or diabetes develops in members of susceptible families, they may develop because of identifiable trigger factors or special varieties of wear and tear. However, in many patients they develop because of changes in metabolism associated with involution and not due to specific external precipitating factors.

When Shakespeare wrote, "Crabbed age and youth cannot live

together" he was, I think, not only pointing out that youth is full of pleasures and age full of care, but also reflecting an old observation that young and old are different kinds of people and may not be happy or well in identical environments. At the same time they may be very good for each other and may indeed be essential for each other.

Some of this difference between old and young appears to be a difference in the rate of living or the rate of energy expenditure. You will remember that at one point in Lewis Carroll's *Through the Looking Glass* the Red Queen seized Alice by the hand and they ran rapidly for a considerable period. At the end of this period Alice observed that they were still under the tree where they had started. She expressed surprise at this and observed that in her country if you ran rapidly for some time you were apt to get somewhere. The Red Queen replied that Alice must come from a slow sort of country and that in her country you had to run that fast to stay in the same place and at least twice that fast if you wanted to get anywhere. Experience indicates that children run, metabolize, and heal their wounds faster than their elders; physiology does not say that by so doing they are necessarily going to get anywhere except to older decades of life.

A more specific and better defined example of variation in a given organism with the passage of time is seen in the fascinating and elegant adjustments that are made in the physiology of a woman when she becomes pregnant. The implantation of the fertilized ovum establishes a new set of requirements. The mother responds by becoming a different organism although certainly and happily still the same woman. As my colleague, Dr. James Metcalfe, has written, "Animal reproduction is enacted by inconvenience on the part of the mother, tenacity on the part of the foetus, and cooperative ingenuity on the parts of both." By this cooperative ingenuity, the fetus is supplied with nutriments, oxygen, and various complex chemical substances such as enzymes, and mechanisms are developed for the disposal of the end products of fetal metabolism.

The adjustments on the part of the maternal organism involve many aspects of physiological function. One change which I was not aware of until relatively recently is an increase in acuity of the sense of smell. To a few women in our experience this is so marked as to be annoying, and in one of our patients this troubling sharpening of sense of smell has occurred in each of four pregnancies. It is interesting to find an

example of this in another species referred to by Chamberlain in his charming book *Bouquet de France; an Epicurean Tour of the French Provinces.* The people of Périgord, it appears, use pigs to seek the truffles which constitute a major resource of this part of France. The pigs find these underground treasures by smelling them, and Chamberlain observes "Small expectant sows are the most competent sniffers."

As the fetus and placenta develop, there occur in the maternal organism extensive alterations in circulation, in ventilation, in the kind and amount of hormones, and in many other mechanisms. We may select as examples more nearly relevant to our discussion some of the alterations in circulation and in ventilation. The volume of blood increases and the cardiac output rises. It is not surprising that during pregnancy these systematic increases in the volume of blood and the cardiac output are observed since it is obvious that the mother's circulation has assumed the new and important duty of transporting materials to and from the fetus. The changes in the circulation are to a considerable degree predictable and have major and sometimes vital implications for the course of heart disease in pregnant women.

Equally impressive changes occur in respiration. One expects that in association with the increased oxygen consumption of the mother there should be an increased ventilation since, as Sherrington says, "The foetus breathes through its mother's blood." It is interesting, however, that the ventilation of the pregnant woman increases sooner and increases more than her oxygen consumption. She actually shows alveolar *hyperventilation* so that the level of carbon dioxide in the arterial blood falls, usually from about 40 mm. to about 30 mm. Hg. This cunning adjustment of carbon dioxide tension permits the fetus to develop at non-toxic levels of carbon dioxide pressure in spite of the substantial gradient of this gas across the placenta.

Now, to change the level of arterial carbon dioxide tension for this nine-month period, some mechanism must be established by the fact of pregnancy. It should be noted that the change in tension takes place early in pregnancy before the oxygen consumption rises measurably, and the change is maintained throughout the course of pregnancy, and that by a few days after delivery the alveolar ventilation has fallen to normal levels in relation to oxygen consumption and the CO_2 has risen to the non-pregnant level. This extraordinary and, from the point of view of the fetus, apparently beneficial adjustment, appears to be due

to actions of progesterone on the respiratory center. This substance is appropriately produced, at least in large part, by the very organ that makes it necessary—namely, the placenta.

Angus MacDonald wrote the first book in English on the relations between heart disease and pregnancy in 1878 and he referred to an observation on the ventilation in pregnant women which is against the expectations of common sense—namely, that the vital capacity of the lungs is not diminished by pregnancy in normal women. In spite of the large tumor filling her abdomen and elevating her diaphragm, some increase in the total lung capacity, plus some invasion of the residual air, enables the pregnant woman to maintain a normal vital capacity and sometimes a slightly enlarged one throughout the course of her pregnancy. The fact that normal women maintain a normal vital capacity during pregnancy does not mean that the tumor of pregnancy is unimportant since in women with kyphoscoliosis and a more rigid rib cage a diminution of vital capacity, sometimes enough to be hazardous, can take place as the uterus increases in size. The maintenance of a normal vital capacity does mean that the pregnant woman by a beneficent provision of nature has increased the capacity of the pulmonary bellows to meet the new demands of a special situation.

Something about pregnancy, perhaps some aspect of the metabolism of estrogens, has profound effects upon the blood vessels of the maternal body. During much of pregnancy we are accustomed to observe a fall in the diastolic blood pressure. The vessels in certain areas of the skin become visibly dilated and the distribution of blood to the skin is obviously altered. In some women changes actually occur in the structure of arterial walls,—changes sufficiently severe so that arterial rupture takes place. This catastrophe when it occurs usually affects arteries which were already abnormal before pregnancy. As examples, consider the dissection of the aortic wall which may take place during pregnancy in patients with coarctation of the aorta; the rupture of berry aneurysms of the circle of Willis, which may occur during pregnancy and the considerable number of ruptures of splenic artery aneurysms which have occurred in pregnant women. These catastrophies do not as a general rule occur under the stress of labor (in spite of a tradition to this effect), but occur most often at the seventh or eighth month of pregnancy. The reasons for this are not yet clear, but the documents are impressive.

In general, changes in maternal physiology occurring with pregnancy are favorable to the survival and development of the fetus. Some of them impose discomforts or hazards upon the mother. When alterations in physiology of the magnitude we have described occur during pregnancy, it is not surprising that a woman when pregnant may react to disease quite differently than when she is non-pregnant. Doctors are familiar with the changes that may occur during pregnancy in the manifestations of rheumatoid arthritis, of diabetes, and of heart disease. Women with long-standing symptoms of duodenal ulcer may become symptom free with the onset of pregnancy. On the other hand, there are women with evidence of duodenal ulcer who bleed from it during pregnancy and not at other times. Those of you who read novels or go to the theatre know from those experiences that fainting may occur during pregnancy and may indeed be the event that calls attention to its existence and announces it to the frightened mother or the happy father. It is now also known that there are patients who have fainted at intervals when not pregnant and who have the curious experience of being free of syncope during pregnancy. In the light of these and other examples it is easy to see and unnecessary to say that to care for disease in a pregnant woman it is essential to understand the physiology of pregnancy as well as that of disease.

The final example of my simple thesis is a phase of life which has been studied too little. This is *sleep*—that agreeable but often forgotten state in which a considerable fraction of our lives is necessarily spent. Sleep is necessary to survival and it tends to recur regularly. Significant physiological changes accompany it and with some of these we shall be concerned. We are discussing what is called natural sleep, not hibernation or narcolepsy or coma. Everyone is aware of sleep as part of life and many observers of life have described it eloquently. Henley wrote:

> "Night with her train of stars
> And her great gift of sleep."

Sir Philip Sidney:

> "Come Sleep! O sleep, the certain knot of peace,
> The baiting place of wit, the balm of woe,
> The poor man's wealth, the prisoner's release,
> Th' indifferent judge between the high and low."

Shakespeare understood some of its physiological effects:

". . . the innocent sleep.
Sleep that knits up the ravell'd sleeve of care,
The death of each day's life, sore labor's bath,
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast."

Not all the references are so filled with approval of sleep. It is also called death's counterfeit and death's twin brother. It should not be called these nor should it be referred to as a state midway between death and life. Sleep is not partial death; it is a different kind of life.

This life is not without its special brand of consciousness, and the study and interpretation of dreams have fascinated mankind for generations. It is said that Dryden supped on raw flesh to obtain splendid dreams, no doubt as a basis for splendid poetry, and the author of "Mysteries of Rudolpho" is said to have eaten the most indigestible substances for the purpose of filling her sleep with phantoms of horror —an occupational hazard for authors.

Sleep is in general admirable, pleasant, and useful. Cervantes had Sancho Panza speak wisely when he said, "We count our blessings on the man who first invented sleep." A modern author, John Godfrey Saxe, has recorded Sancho Panza's attitude and added some comments of his own in the following stirring verse:

" 'God bless the man who first invented sleep!'
So Sancho Panza said, and so say I:
And bless him, also, that he didn't keep
His great discovery to himself; nor try
To make it—as the lucky fellow might—
A close monopoly by patent right!

"Yes, bless the man who first invented sleep
(I really can't avoid the iteration)
But blast the man with curses loud and deep
What e'er the rascal's name, or age, or station
Who first invented and went round advising
That artificial cut off—Early Rising."

However pleasant these comments and reflections of others may be, they are not our present duty. Let us consider some characteristics of

sleep and some of the physiological changes which are known to accompany it. Many of the characteristic physiological differences between the waking and sleeping individual come on rapidly with the change from one to the other. Some of them occur, as we shall see, in a matter of seconds. Most of the changes that we know about are not the cause of sleep. They are associated with the fact of sleep. In a sleeping person, for example, there is a widespread muscular relaxation, a diminution in body temperature, and characteristic changes in the electroencephalogram. Oxygen consumption falls and so does the production of CO_2. In spite of diminution in the production of CO_2, the level of carbon dioxide in the alveolar air and in the arterial blood rises. It rises significantly, as much as 5 or 10 mm. Hg. This is just the opposite of what occurs in the pregnant woman. It is another example of a natural event leading to the establishment of a new equilibrium in a vital and consistent physiological measurement.

This rise in carbon dioxide tension is due to alveolar *hypo*ventilation as the fall in carbon dioxide tension in pregnant women is due to alveolar *hyper*ventilation. The hypoventilation of sleep is apparently related to an alteration in the sensitivity of the respiratory center to the stimulus of carbon dioxide. This change in sensitivity can be demonstrated by observing the effects of inhaled carbon dioxide on sleeping persons. An interesting aspect of this matter is that this change in sensitivity occurs with amazing rapidity and is demonstrable a few seconds after the onset of sleep.

This diminished sensitivity of the respiratory center during sleep is probably one of the reasons why periodic respiration occurs in some normal people during sleep, and why during sleep patients with heart or pulmonary disease may show a marked accentuation of a previous existing periodicity. Indeed, sleep may be a time of increased abnormality in patients with some varieties of disease, especially those who already have an elevated carbon dioxide tension. When to the elevated carbon dioxide of disease is added a further elevation due to sleep, a further and potentially harmful depression of the respiratory center may ensue.

Physicians have long been interested in the variations and the manifestations of disease between sleeping and waking. One example will suffice. Paroxysmal nocturnal hemoglobinuria is a disease characterized by the presence of abnormal erythrocytes which undergo hemolysis

more easily than do normal red cells. This increased hemolysis takes place under special conditions. The most frequently recognized situation associated with increased hemolysis is the sleeping state. These patients usually show a peak of plasma hemoglobin levels between one and four o'clock in the morning, and the morning urine contains the largest amount of the hemoglobin which they excrete during a 24-hour period.

If these patients sleep during the day and work during the night, they reverse the pattern of hemolysis so that now the major portion of hemolysis takes place during the daytime hours.

Cells from these patients, studied *in vitro*, hemolyze in acid media, but it has been demonstrated that the modest respiratory acidosis that develops during sleep is not responsible for the increased hemolysis during this state. Nor is the increased carbon dioxide of sleep responsible since much higher levels of CO_2 can be imposed on the red cells without inducing hemolysis. The metabolic change which produces the disorder is not known, but it is something which accompanies sleep and makes us want to know much more about the physiology of this important part of our lives.

Summary

These rather rambling reflections may remind us that as physicians we deal not with an invariable or monotonous organism, but one which while basically stable still shows fascinating, important, and to some degree predictable variations. These variations are not in the eye of the beholder, but in the patient. In our interpretation and management of disease, we are accustomed to recognize and control many factors in the external environment, such as temperature, dust, pathogenic organisms, insects, noise, the gas content of the inhaled air, and the ambient emotions. We have also to realize that comparable variations occur in the internal environment due to changes in the pattern of homeostasis associated with such natural events as growth, development, pregnancy, and sleep.

Certain examples of such changes have been presented. It has been possible to show, for example, that the carbon dioxide tension of the arterial blood falls during pregnancy and rises during sleep. The first change is apparently based on a hormonal mechanism; the second on a neural mechanism. As far as the available evidence goes, the aging

process is not associated with comparable changes in carbon dioxide tension although it is associated with progressive changes in certain quantitative aspects of ventilation. This presumably means that the basic mechanism for the maintenance of a more or less standard level of carbon dioxide in the arterial blood is not altered by the progressive changes of involution, whereas the non-permanent changes in pregnancy and sleep do alter the controlling mechanism so as to reset this level for the duration of these states.

Therefore, as the mathematician may think of time as a fourth dimension added to space, we, as physicians, may think of time as an additional definition often significant in patients.

This discussion has emphasized the factor of change in the human organism. It would not be fair to conclude it without reminding you that the changes we have been discussing happily occur without destroying identity. Let us be thankful that this durable and tenacious organism, which is the basis of our life and happiness, not only exhibits the fascinating changes we have discussed, but it exhibits also a wonderful and vital continuity. In the changes imposed by the natural events of life, individuality is not lost and our friends are still our friends though they may be old, or pregnant, or asleep.